UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,307	01/14/2004	Melody A. Cobleigh	39740-0008A	5600

25213 7590 07/11/2008

HELLER EHRMAN LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, CA 92122

EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
07/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,307	COBLEIGH ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,8,9,25-28,30,36,37,53 and 56-66* is/are pending in the application.

4a) Of the above claim(s) *56-63,65 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,8,9,25-28,30,36,37,53 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 6, 8, 9, 25-28, 30, 36, 37, 53, 56-66 are pending in the application.

This Office Action is in response to the amendment filed on 2/19/08.

Response to Amendment

All previous rejections that are not reiterated in this office action are considered withdrawn.

Election/Restrictions

Applicants assert that once claims 1 and 25 becomes allowed, claims 56-63 will be rejoined as a result of their dependence from claim 1 and 25.

The examiner acknowledges that the restriction requirement mailed on 9/26/06 states that all claims which have been restricted and non-selected and which are limited to the allowable sequences will be rejoined and examined, and all combination containing the allowable sequences and any patentably indistinct sequences will be rejoined and allowed. Since claims 1 and 25 are not allowed, claims 56-63 are withdrawn from consideration.

Newly submitted claims 65 and 66 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The report provide prognostic information to an ER positive breast cancer patient can be generated by other method, such as writing a review article based on known data, or the report may be a computer database comprises information with regard to MYBL2 expression in breast cancer cells. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, although the report may be related to the method of

predicting the likelihood of survival of a ER+ patient, it is not made by said method. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Therefore, the elected method is patentably distinct from the report claimed by claims 65 and 66.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 65 and 66 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 8, 9, 25-28, 30, 36, 37, 53 and 64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use

the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention

The claimed invention is drawn to a method of predicting the likelihood of long-term survival of a breast cancer patient without the recurrence of breast cancer, comprising determining the expression level MYBL2, wherein the expression of MYBL2 indicates a decreased likelihood of long-term survival without breast cancer recurrence.

The breadth of the claim

The breadth of the claim is rather broad. The broadest claim encompasses a method of predicting longer-term survival of a patient with ER+ breast cancer, and with or without any treatment by the mere presence of MYBL2 expression of both mRNA and protein. Claim 30 further comprises a step of making a recommendation for a treatment modality of the patient. Although the name MYBL2 refer to a protein, myeloblastosis oncogene-like 2, it also encompasses orthologs wherein the sequences are substantially different from each other (see attached MYBL2 search result) and splice variants which may exist, but their full length nature have not been determined (see NCBI sequence NM_002466 description on page 2, see attached).

The teaching of the specification and the working examples provided

The specification teaches based on binary statistical analysis, MYBL2, presumably the sequence disclosed as NM_002466 since it is listed in Table 5C, is determined to have higher expression (Table 2) of mRNA in invasive breast carcinoma which is ER positive than that breast carcinoma with no death or recurrence 3 year following surgery. The specification discloses the

mean expression value of patients with death or recurrence is higher than those patients with no recurrence or death (see Table 2), thereby establishing a correlation between breast cancer recurrence or death and the higher expression of the mRNA transcripts of the sequence disclosed in NM_002466. However, the specification does not establish the mere expression of this transcript is indicative of a decreased likelihood of long-term survival without breast cancer recurrence because it appears that MYBL2 taken from the tumor sample of survival patient also has positive expression. Moreover, the specification does not teach whether this correlation is also observed at protein level. As such, whether the expression of MYBL2, including any splice variants or protein product, is indicative of poor prognosis in ER+ breast cancer is unpredictable.

The state of prior art and the level of predictability in the art

The prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test. Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph [0156]). Shalon et al teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph [0158]). Post filing art, Kroese et al

(Genetics in Medicine, Vol. 6, pages. 475-480, 2004) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (e.g. page 476, 2nd column, last paragraph). Kroese et al teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (e.g. page 477, 1st column, 1st and 2nd full paragraph). Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (e.g. page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, Vol. 18, page 20, 2004) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (e.g. page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (e.g. page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (e.g. page 3, 2nd paragraph).

As indicated in a review article written by Murphy et al. (Pathology, 2005, Vol 37(4), pages 271-277), the use of gene expression profiling in breast cancer prognostication and prediction has

not yet reached the stage where it can be implemented clinically (see page 275, 2nd col., 2nd paragraph). Murphy et al. assert "an array of confounding issues remains, including differences in patient selection, array technology and chemistry, and methods of analysis" and "validation of new markers must be performed in the context of perspective clinical trials in which the prognostic or predictive questions can be answered." Korfee et al. (Current Pharmacogenomics, 2005. Vol.3, pp.201-216) teach that expression level determined at mRNA level does not always correlate to protein level, sometimes even demonstrate conflicting results (see page 214, 1st col., 1st full paragraph, lines 28-49). Korfee et al. also indicate that although good or poor prognosis signature may be established in laboratory, the clinical outcome is unpredictable at present (see page 204, 1st col., 1st paragraph).

The experimentation required to practice the claimed method

In summary, use of gene profiling in breast cancer prognostication is still under active investigation wherein validation of the test is very important. The instant specification discloses a correlation of higher MYBL2 expression at mRNA level in breast tumor with recurrence than that of breast tumors with no recurrence 3 years following surgery. However, the specification fails to teach whether such correlation also exist at protein level. Moreover, the specification fails to teach whether mere expression of the MYBL2 in tumor sample is indicative of poor prognosis. In terms of recommendation of treatment, the specification does not teach what sort of treatment is recommended based on the expression of MYBL2. In terms of claim 53, the specification does not teach how the reference control cancer sample is chosen. Since the state of prior art teaches that using gene expression signature to provide prognosis in breast cancer is still an unpredictable in the

art, one of skilled in the art would have to engage in undue experimentation to practice the method as claimed. Therefore, the claimed method is not enabled by the instant specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joe Woitach Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian Ph.D./
Primary Examiner, Art Unit 1636